Refine Search

Search Results -

Terms	Documents
L1 and mm2	1

Database:
- US Pre-Grant Publication Full-Text Database
- US Patents Full-Text Database
- US OCR Full-Text Database
- EPO Abstracts Database
- JPO Abstracts Database
- Derwent World Patents Index
- IBM Technical Disclosure Bulletins

Search: L5

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Wednesday, July 14, 2004 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT; PLUR=YES; OP=AND			
L5	l1 and mm2	1	L5
L4	l1 with l2	0	L4
L3	l1 and L2	160	L3
L2	mm or mm2	788077	L2
L1	(adeno-associated adj virus or aav or raav) near7 (brain or cns or nervous adj system or striatum or cerebrum or cerebellum or hippocampus)	181	L1

END OF SEARCH HISTORY

h e b b cg b e e ch

Generate Collection | Print

Search Results - Record(s) 1 through 1 of 1 returned.

☐ 1. 20030216335. 27 Nov 02. 20 Nov 03. Method and reagent for the modulation of female reproductive diseases and conditions. Lockridge, Jennifer, et al. 514/44; A61K048/00.

Generate Collection | Print

Terms	Documents
L1 and mm2	1

Prev Page Next Page Go to Doc#

h e b b g e e e f e e e e eh che

09/887,854

```
=> s (adeno-associated(w)virus or aav or raav)(7a)(brain or cns or nervous(w)system
or striatum or cerebrum or cerebellum or hippocampus)
L1          529 (ADENO-ASSOCIATED(W) VIRUS OR AAV OR RAAV)(7A)(BRAIN OR CNS OR
                NERVOUS(W) SYSTEM OR STRIATUM OR CEREBRUM OR CEREBELLUM OR HIPPO
                CAMPUS)

=> s mm or mm2
L2      1644646 MM OR MM2

=> s l1 and l2
L3           10 L1 AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            9 DUP REM L3 (1 DUPLICATE REMOVED)

=> d his

     (FILE 'HOME' ENTERED AT 18:51:29 ON 14 JUL 2004)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 18:52:17 ON 14 JUL
     2004
L1          529 S (ADENO-ASSOCIATED(W)VIRUS OR AAV OR RAAV)(7A)(BRAIN OR CNS OR
L2      1644646 S MM OR MM2
L3           10 S L1 AND L2
L4            9 DUP REM L3 (1 DUPLICATE REMOVED)

=> d au ti so pi ab 1-9 l4

L4   ANSWER 1 OF 9     MEDLINE on STN                          DUPLICATE 1
AU   Hadaczek Piotr; Mirek Hanna; Bringas John; Cunningham Janet; Bankiewicz
     Krys
TI   Basic fibroblast growth factor enhances transduction, distribution, and
     axonal transport of adeno-associated virus
     type 2 vector in rat brain.
SO   Human gene therapy, (2004 May) 15 (5) 469-79.
     Journal code: 9008950. ISSN: 1043-0342.
AB   The ubiquitous expression of cell surface heparan sulfate proteoglycan, a
     binding receptor for adeno-associated virus type 2 (AAV-2), may account
     for the broad host range of this vector. Because the fibroblast growth
     factor receptor type 1 has been postulated to be a coreceptor for
     successful AAV-2 entry into host cells, we designed a strategy to
     investigate whether coadministration of this virus with basic fibroblast
     growth factor (bFGF) can enhance AAV-2-mediated gene delivery. We
     injected AAV-2-thymidine kinase (AAV-2-TK) vector into rat striata and
     checked whether coinjection with bFGF enhanced transduction and/or
     enlarged the area of transgene expression. Immunostaining confirmed the
     tropism of AAV-2-TK for neurons. The previous injection (7 days before
     vector delivery) of bFGF had no major impact on vector distribution area.
     However, when the vector was coinjected with bFGF, the right striatum
     showed an average viral transduction volume of 5 mm(3), which
     was more than 4-fold larger when compared with the left side (AAV-2-TK
     plus phosphate-buffered saline). This result clearly indicates that
     simultaneous injection of bFGF with AAV-2-TK can greatly enhance the
     volume of transduced tissue, probably by way of a competitive block of
     AAV-2-binding sites within the striatum. Robust TK
     immunoreactivity was also observed in the globus pallidus, which receives
     anterograde projections from the striatum. We propose that postsynaptic
     transport of recombinant particles was likely responsible for the
     distribution of TK in the globus pallidus on both bFGF-treated and
     untreated sides. In summary, we found that bFGF acts as an adjuvant for
     distribution of AAV-2 in rat brain.

L4   ANSWER 2 OF 9  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
```

AU Sanftner L M (Reprint); Suzuki B M; Doroudchi M M; Feng L; McClelland A; Forsayeth J R; Cunningham J

TI Striatal delivery of rAAV-hAADC to rats with preexisting immunity to AAV

SO MOLECULAR THERAPY, (MAR 2004) Vol. 9, No. 3, pp. 403-409.
Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
ISSN: 1525-0016.

AB We tested the hypotheses that initial immunization of rats with rAAV might limit subsequent transduction by **rAAV**-hAADC when sterecitaxically infused into the **striatum** and that the level of inhibition would correlate with AAV neutralizing antibody titers. Immunohistochemical detection of AADC and analysis by stereology revealed that the control group (no immunization) had the greatest volume of distribution of AADC (20.32 +/- 2.03 **mm**(3)) (+/-SD). There was a 58% decrease in spread (8.46 +/- 3.67 **mm**(3), $P < 0.008$) in the high-dose immunization group (5 x 10(10) vg rAAV-null). Transduction weakly correlated with preexisting titer levels of neutralizing antibody at the time of intrastriatal rAAV-hAADC infusion. Only rats with neutralizing antibody titers of 1: 1208 332 had significantly decreased AADC transgene expression compared to the unimmunized control group. Immunohistochemistry on serial sections for inflammatory markers including CFAP, CD11b, CD4, and CD8a revealed normal morphology and no cellular infiltration, suggesting little immune reaction in the **CNS**. We conclude that **rAAV** vectors can transduce **brain** tissue in the context of preexisting immunity, but that efficiency of transduction declines significantly in the presence of very high titers of neutralizing antibodies. These results have important implications for gene therapy for CNS disorders.

L4 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AU Xu, Y. [Reprint Author]; Wang, L.; Uy, M. I.; Li, J.; Wang, B.; Zhou, L.; Xiao, X.

TI Widespread gene delivery and expression in adult mouse **brain** by recombinant **adeno - associated virus** for potential gene therapy of ischemic injuries in selective vulnerable regions.

SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 861.9. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.

AB Many disseminated neurological disorders are potentially manageable by gene therapy. Widespread somatic gene transfer in adult CNS by systemic delivery and without irradiation has not been documented. We report here the successful use of recombinant adeno-associated virus serotype-5 (rAAV5) vectors for widespread delivery of the beta-galactosidase (beta-gal) reporter expression cassette and brain-derived neurotrophic factor (BDNF) into the adult mouse brain.Intraventricular microinjection was performed using a microprocessor-driven syringe pump at a rate comparable to the flow of the cerebral spinal fluid. Nine to 35 days after injection, widespread beta-gal expression can be found in the hippocampal CA1, CA3, dentate gyrus, subventricular zone, indusium griseum, lateral entorhinal cortex, and septal regions. The beta-gal positive cells were detected in a wide span of 5.74 **mm** in the rostral-caudal direction. The pattern of BDNF expression is very similar. A slight shift of the injection site to the more posterior location extended the transgene expression to thalamus, hypothalamus, and dorsal lateral geniculate regions. Quantitative analysis suggests that the percentage of the infected cells varies with brain regions and anatomic structures. Immunohistostaining and co-localization show that most of the positively stained cells are neurons.We conclude that 1) widespread gene delivery to the central nervous system is possible with rAAV5; 2) the transgene expressions are predominantly in neurons; 3) the transgene distribution pattern depends on the injection site; and 4) there is a significant level of expression in the contralateral side of the

injection, suggesting a transgene migration to locations remote from the injection site.

L4 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AU Richichi, C. [Reprint Author]; Lin, D. E.; Moneta, D. [Reprint Author]; Colella, D. [Reprint Author]; Aliprandi, M. [Reprint Author]; Stefanin, D. [Reprint Author]; Grignaschi, G. [Reprint Author]; Zennaro, E. [Reprint Author]; Vezzani, A. [Reprint Author]; During, M. J.
TI ADENO - ASSOCIATED VIRAL VECTOR (RAAV) CARRYING THE NEUROPEPTIDE Y GENE INDUCES LONG - LASTING PEPTIDE TRANSDUCTION IN RAT HIPPOCAMPUS AND INHIBITS LIMBIC SEIZURES.
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 603.12. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
AB We investigated the effect of NPY overexpression in the rat **hippocampus** on limbic seizures using an **rAAV** vector carrying the NPY gene (2 1 AAV-NPY, 4.2x108). Transgene expression was maximal 4 weeks after its intrahippocampal delivery and lasted for about 6 months, as assessed by in situ hybridization analysis of NPY mRNA and peptide immunostaining. NPY specifically increased in hilar interneurons and their axonal projections. Immunofluorescence using green fluorescence protein as a reporter gene, showed that the rAAV spreads for about 2 **mm** from its injection site. Rats injected 2.5 months before with rAAV-NPY both in septal and temporal poles of the hippocampus bilaterally had less EEG seizures induced by intrahippocampal injection of 40 ng kainic acid. Thus, the number of seizures (25 5, n=5) and the duration of seizures (24.5 3.2 min) in AAV-empty cassette injected rats was reduced by 2-fold on average ($p<0.01$). After intracerebroventricular injection of 250 ng kainic acid, only the onset of EEG seizures was significantly delayed by 2-fold ($p<0.01$) in rats pre-injected with rAAV-NPY as before. Thus, rAAV mediated long-term transduction of NPY into hilar interneurons inhibits seizures or delays their onset depending on their way of induction. This suggests that chronic increase of an inhibitory peptide in crucial brain sites may represent a novel strategy for antiepileptic treatment.

L4 ANSWER 5 OF 9 MEDLINE on STN
AU During M J; Kaplitt M G; Stern M B; Eidelberg D
TI Subthalamic GAD gene transfer in Parkinson disease patients who are candidates for deep brain stimulation.
SO Human gene therapy, (2001 Aug 10) 12 (12) 1589-91. Journal code: 9008950. ISSN: 1043-0342.
AB This gene transfer experiment is the first Parkinson's Disease (PD) protocol to be submitted to the Recombinant DNA Advisory Committee. The principal investigators have uniquely focused their careers on both pre-clinical work on gene transfer in the brain and clinical expertise in management and surgical treatment of patients with PD. They have extensively used rodent models of PD for proof-of-principle experiments on the utility of different vector systems. PD is an excellent target for gene therapy, because it is a complex acquired disease of unknown etiology (apart from some rare familial cases) yet it is characterized by a specific neuroanatomical pathology, the degeneration of dopamine neurons of the substantia nigra (SN) with loss of dopamine input to the striatum. This pathology results in focal changes in the function of several deep brain nuclei, which have been well-characterized in humans and animal models and which account for many of the motor symptoms of PD. Our original approaches, largely to validate in vivo gene transfer in the brain, were designed to facilitate dopamine transmission in the **striatum** using an **AAV** vector expressing dopamine-synthetic enzymes. Although these confirmed the safety and potential efficacy of AAV, complex patient responses to dopamine augmenting medication as well as poor results and complications of human transplant studies suggested that this would be a difficult and

potentially dangerous clinical strategy using current approaches. Subsequently, we and others investigated the use of growth factors, including GDNF. These showed some encouraging effects on dopamine neuron survival and regeneration in both rodent and primate models; however, uncertain consequences of long-term growth factor expression and question regarding timing of therapy in the disease course must be resolved before any clinical study can be contemplated. We now propose to infuse into the subthalamic nucleus (STN) recombinant AAV vectors expressing the two isoforms of the enzyme glutamic acid decarboxylase (GAD-65 and GAD-67), which synthesizes the major inhibitory neurotransmitter in the brain, GABA. The STN is a very small nucleus (140 cubic mm or 0.02% of the total brain volume, consisting of approximately 300,000 neurons) which is disinhibited in PD, leading to pathological excitation of its targets, the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). Increased GPi/SNpr outflow is believed responsible for many of the cardinal symptoms of PD, i.e., tremor, rigidity, bradykinesia, and gait disturbance. A large amount of data based on lesioning, electrical stimulation, and local drug infusion studies with GABA-agonists in human PD patients have reinforced this circuit model of PD and the central role of the STN. Moreover, the closest conventional surgical intervention to our proposal, deep brain stimulation (DBS) of the STN, has shown remarkable efficacy in even late stage PD, unlike the early failures associated with recombinant GDNF infusion or cell transplantation approaches in PD. We believe that our gene transfer strategy will not only palliate symptoms by inhibiting STN activity, as with DBS, but we also have evidence that the vector converts excitatory STN projections to inhibitory projections. This additional dampening of outflow GPi/SNpr outflow may provide an additional advantage over DBS. Moreover, of perhaps the greatest interest, our preclinical data suggests that this strategy may also be neuroprotective, so this therapy may slow the degeneration of dopaminergic neurons. We will use both GAD isoforms since both are typically expressed in inhibitory neurons in the brain, and our data suggest that the combination of both isoforms is likely to be most beneficial. Our preclinical data includes three model systems: (1) old, chronically lesioned parkinsonian rats in which intraSTN GAD gene transfer results not only in improvement in both drug-induced asymmetrical behavior (apomorphine symmetrical rotations), but also in spontaneous behaviors. In our second model, GAD gene transfer precedes the generation of a dopamine lesion. Here GAD gene transfer showed remarkable neuroprotection. Finally, we carried out a study where GAD-65 and GAD-67 were used separately in monkeys that were resistant to MPTP lesioning and hence showed minimal symptomatology. Nevertheless GAD gene transfer showed no adverse effects and small improvements in both Parkinson rating scales and activity measures were obtained. In the proposed clinical trial, all patients will have met criteria for and will have given consent for STN DBS elective surgery. Twenty patients will all receive DBS electrodes, but in addition they will be randomized into two groups, to receive either a solution containing rAAV-GAD, or a solution which consists just of the vector vehicle, physiological saline. Patients, care providers, and physicians will be blind as to which solution any one patient receives. All patients, regardless of group, will agree to not have the DBS activated until the completion and unblinding of the study. Patients will be assessed with a core clinical assessment program modeled on the CAPSIT, and in addition will also undergo a preop and several postop PET scans. At the conclusion of the study, if any patient with sufficient symptomatic improvement will be offered DBS removal if they so desire. Any patients with no benefit will simply have their stimulators activated, which would normally be appropriate therapy for them and which requires no additional operations. If any unforeseen symptoms occur from STN production of GABA, this might be controlled by blocking STN GABA release with DBS, or STN lesioning could be performed using the DBS electrode. Again, this treatment would not subject the patient to additional invasive brain surgery. The trial described here reflects an evolution in our thinking about the best

strategy to make a positive impact in Parkinson Disease by minimizing risk and maximizing potential benefit. To our knowledge, this proposal represents the first truly blinded, completely controlled gene or cell therapy study in the brain, which still provides the patient with the same surgical procedure which they would normally receive and should not subject the patient to additional surgical procedures regardless of the success or failure of the study. This study first and foremost aims to maximally serve the safety interests of the individual patient while simultaneously serving the public interest in rigorously determining in a scientific fashion if gene therapy can be effective to any degree in treating Parkinson's disease.

L4 ANSWER 6 OF 9 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AU Cunningham J; Oiwa Y; Nagy D; Podsakoff G; Colosi P; Bankiewicz K S (Reprint)
TI Distribution of AAV-TK following intracranial convection-enhanced delivery into rats
SO CELL TRANSPLANTATION, (SEP-OCT 2000) Vol. 9, No. 5, pp. 585-594. Publisher: COGNIZANT COMMUNICATION CORP, 3 HARTSDALE ROAD, ELMSFORD, NY 10523-3701.
ISSN: 0963-6897.
AB Adeno-associated virus (AAV)-based vectors are being tested in animal models as viable treatments for glioma and neurodegenerative disease and could potentially be employed to target a variety of central nervous system disorders. The relationship between dose of injected vector and its resulting distribution in brain tissue has not been previously reported nor has the most efficient method of delivery been determined. Hen we report that convection-enhanced delivery (CED) of 2.5 x 10(8), 2.5 x 10(9), or 2.5 x 10(10) particles of **AAV**-thymidine kinase (**AAV**-TK) into rat **brain** revealed a clear dose response. In the high-dose group, a volume of 300 **mm**(3) of brain tissue was partially transduced. Results showed that infusion pump and subcutaneous osmotic pumps were both capable of delivering vector via CED and that total particle number was the most important determining factor in obtaining efficient expression. Results further showed differences in histopathology between the delivery groups. While administration of vector using. infusion pump had relatively benign effects, the use of osmotic pumps resulted in notable toxicity to the surrounding brain tissue. To determine tissue distribution of vector following intracranial delivery, PCR analysis was performed on tissues from rats that received high doses of AAV-TK. three weeks following CED, vector could be detected in both hemispheres of the brain, spinal cord, spleen, and kidney.

L4 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AU Passini, M. A. [Reprint author]; Lee, E. B.; Crystal, A.; Wolfe, J. H.
TI The human B-glucuronidase promoter provides long-term expression from an adeno-associated viral vector following in vivo injections of multiple brain structures.
SO Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-668.8. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
AB The site and duration of gene expression from adeno-associated virus (AAV) vectors vary in different regions of the adult mouse brain. This observation may be a result of differences in the ability of specific brain regions to utilize the promoter driving gene expression. Thus, we analyzed the behavior of an AAV vector under the control of an ubiquitously expressed CNS promoter to understand its potential as a long-term global expresser of exogenous genes. An AAV construct containing the human B-Glucuronidase (GUSB) promoter upstream of the human GUSB cDNA was engineered and injected into multiple brain regions in adult mice. Strong mRNA expression and enzyme activity were detected 3-5 months after viral administration in the cortex, hippocampus, subiculum,

striatum, substantia nigra, hypothalamus, thalamus, and cerebellum. Transduced cells, as determined by in situ hybridization, remained confined to the injection site. However, when analyzing exogenous enzyme activity, cells were detected in the in situ positive regions and in areas located 3 **mm** away from the injection site. A feature of GUSB and most other lysosomal storage enzymes is that they can be secreted by normal cells and taken up by mutant cells in a process called cross correction. This data demonstrates that a single administration of **AAV** in the **brain** can lead to widespread enzyme delivery, and that differences in AAV vector expression exists in different structures of the adult mouse brain.

L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
AU Mandel, R. J.; Rendahl, K. G.; Spratt, S. K.; Snyder, R. O.; Cohen, L. K.; Leff, S. E.
TI Characterization of intrastriatal recombinant adeno-associated virus-mediated gene transfer of human tyrosine hydroxylase and human GTP-cyclohydrolase I in a rat model of Parkinson's disease
SO Journal of Neuroscience (1998), 18(11), 4271-4284
CODEN: JNRSDS; ISSN: 0270-6474
AB To achieve local, continuous L-DOPA delivery in the striatum by gene replacement as a model for a gene therapy for Parkinson's disease, the present studies used high titer purified recombinant adeno-associated virus (rAAV) containing cDNAs encoding human tyrosine hydroxylase (hTH) or human GTP-cyclohydrolase I [GTPCHI, the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis] or both to infect the 6-OHDA denervated rat striatum. Striatal TH and GTPCHI staining was observed 3 wk after rAAV transduction, with little detectable perturbation of the tissue. Six months after intrastriatal rAAV transduction, TH staining was present but apparently reduced compared with the 3 wk survival time. In a sep. group of animals, striatal TH staining was demonstrated 1 yr after rAAV transduction. Double staining studies using the neuronal marker NeuN indicated that >90% of rAAV-transduced cells expressing hTH were neurons. Microdialysis expts. indicated that only those lesioned animals that received the mixture of MD-TH and MD-GTPCHI vector displayed BH4 independent in vivo L-DOPA production (mean .apprx.4-7 ng/mL). Rats that received the hTH rAAV vector alone produced measurable L-DOPA (mean .apprx.1-4 ng/mL) only after receiving exogenous BH4. L-Aromatic amino acid decarboxylase blockade, but not 100 **mM** KCl-induced depolarization, enhanced L-DOPA overflow, and animals in the non-hTH groups (GTPCHI and alkaline phosphatase) yielded minimal L-DOPA. Although elevated L-DOPA was observed in animals that received mixed hTH and hGTPCHI rAAV vectors, there was no reduction of apomorphine-induced rotational behavior 3 wk after intrastriatal vector injection. These data demonstrate that purified rAAV, a safe and nonpathogenic viral vector, mediates long-term striatal hTH transgene expression in neurons and can be used to successfully deliver L-DOPA to the striatum.

L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
AU Okada, H.; Miyamura, K.; Itoh, T.; Hagiwara, M.; Wakabayashi, T.; Mizuno, M.; Colosi, P.; Kurtzman, G.; Yoshida, J.
TI Gene therapy against an experimental glioma using adeno-associated virus vectors
SO Gene Therapy (1996), 3(11), 957-964
CODEN: GETHEC; ISSN: 0969-7128
AB The efficacy of gene therapy for glioma was examined using adeno-associated virus (AAV)-based vectors to deliver genes to exptl. tumors in mice. Stereotactic injection of 2+105 U-251SP human glioma cells into the brains of nude mice produced tumors of 19.06 ± 1.79 **mm2** 17 days after injection. Employing a high titer preparation of AAV vector containing the gene for β-galactosidase (AAV-lacZ), dose-dependent transduction of U-251SP cells was seen in vitro. When 1.6 + 1010 AAV-lacZ particles were directly injected into tumors in vivo, 30-40% of the cells

along the needle track expressed β-galactosidase. Transduction of U-251SP cells in vitro with an AAV vector containing a bicistronic gene encoding both herpes simplex thymidine kinase and human interleukin-2 (AAV-tk-IRES-IL2) rendered them sensitive to the cytocidal effects of ganciclovir (GCV) and IL-2 was produced in a dose-dependent manner. Cocultures of AAV-tk-IRES-IL2 transduced cells and nontransduced cells proved highly sensitive to GCV indicating the contribution of the bystander effect. Stero-tactic delivery of 6 + 1010 AAV-tk-IRES-IL2 particles into day 7 tumors in nude mice followed by administration of GCV for 6 days, resulted in a 35-fold reduction in the mean volume of tumors compared with controls. Normal brains did not suffer from any toxic effect of the administration of AAV-tk-IRES-IL2 and GCV. These results indicate that high titer AAV vector treatment may be safe and effective for in vivo gene therapy of human brain tumors.

=>

09/887,854

```
=> d his

     (FILE 'HOME' ENTERED AT 11:17:27 ON 14 MAY 2004)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 11:17:59 ON 14 MAY
     2004
L1        16660 S (INFUSION OR OSMOTIC)(3A)PUMP
L2        10034 S ADENO-ASSOCIATED(W)(VIRUS OR VIRAL)
L3           15 S L1 AND L2
L4           11 DUP REM L3 (4 DUPLICATES REMOVED)

=> d bib ab 1-11 l4

L4   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2003:173806  CAPLUS
DN   138:180748
TI   Use of adeno-associated virus vectors for
     delivery of mammalian glial-derived neutrophic factor genes for treatment
     of neurodegenerative diseases
IN   Ozawa, Keiya; Muramatsu, Shin-ichi
PA   Ikeguchi, Kunihiko, Japan; Nakano, Imaharu
SO   PCT Int. Appl., 75 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 2003018821      A2    20030306      WO 2002-JP8761   20020829
     WO 2003018821      A3    20031030
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
            PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
            UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
            RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
            CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
            PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
            NE, SN, TD, TG
     US 2003050273      A1    20030313      US 2002-230875   20020828
PRAI US 2001-315838P    P     20010829
AB   Compns. and methods for treating subjects with preexisting neuronal damage
     are disclosed. The compns. and methods use adeno-assocd
     . virus (AAV)-based gene delivery systems for delivering glial
     cell line-derived neutrophic factor (GDNF) to subjects with
     neurodegenerative conditions such as Parkinson's disease.

L4   ANSWER 2 OF 11     MEDLINE on STN
AN   2003545726     MEDLINE
DN   PubMed ID: 14625141
TI   Brain-derived neurotrophic factor in the ventral midbrain-nucleus
     accumbens pathway: a role in depression.
AU   Eisch Amelia J; Bolanos Carlos A; de Wit Joris; Simonak Ryan D; Pudiak
     Cindy M; Barrot Michel; Verhaagen Joost; Nestler Eric J
CS   Department of Psychiatry, The University of Texas Southwestern Medical
     Center, Texas, Dallas 75390-9070, USA.
SO   Biological psychiatry, (2003 Nov 15) 54 (10) 994-1005.
     Journal code: 0213264. ISSN: 0006-3223.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
```

FS Priority Journals
EM 200312
ED Entered STN: 20031120
Last Updated on STN: 20031230
Entered Medline: 20031229
AB BACKGROUND: Previous work has shown that brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase receptor B (TrkB), are involved in appetitive behavior. Here we show that BDNF in the ventral tegmental area-nucleus accumbens (VTA-NAc) pathway is also involved in the development of a depression-like phenotype. METHODS: Brain-derived neurotrophic factor signaling in the VTA-NAc pathway was altered in two complementary ways. One group of rats received intra-VTA infusion of vehicle or BDNF for 1 week. A second group of rats received intra-NAc injections of vehicle or **adeno-associated viral** vectors encoding full-length (TrkB.FL) or truncated (TrkB.T1) TrkB; the latter is kinase deficient and serves as a dominant-negative receptor. Rats were examined in the forced swim test and other behavioral tests. RESULTS: Intra-VTA infusions of BDNF resulted in 57% shorter latency to immobility relative to control animals, a depression-like effect. Intra-NAc injections of TrkB.T1 resulted in and almost fivefold longer latency to immobility relative to TrkB.FL and control animals, an antidepressant-like effect. No effect on anxiety-like behaviors or locomotion was seen. CONCLUSIONS: These data suggest that BDNF action in the VTA-NAc pathway might be related to development of a depression-like phenotype. This interpretation is intriguing in that it suggests a role for BDNF in the VTA-NAc that is opposite of the proposed role for BDNF in the hippocampus.

L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:52003 CAPLUS
DN 136:117371
TI Method of inducing an immunological CTL response by lymphatic system delivery of peptide vaccine
IN Kundig, Thomas M.; Simard, John J. L.
PA Switz.
SO U.S. Pat. Appl. Publ., 48 pp., Cont.-in-part of U. S. Ser. No. 380,534.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002007173	A1	20020117	US 2001-776232	20010202
	WO 9902183	A2	19990121	WO 1998-US14289	19980710
	WO 9902183	A3	19990514		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	AU 2001097432	A5	20020808	AU 2001-97432	20011221
	WO 2002062368	A2	20020815	WO 2002-US2033	20020122
	WO 2002062368	A3	20030925		
	WO 2002062368	C1	20031120		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2003138808	A1	20030724	US 2002-225568	20020820
PRAI	CA 1997-2209815	A	19970710		
	US 1997-988320	B2	19971210		
	WO 1998-US14289	W	19980710		
	US 1999-380534	A2	19990901		
	US 1998-26066	A2	19980219		
	US 2000-561572	A2	20000428		
	US 2000-715835	A2	20001116		
	US 2001-776232	A	20010202		
	US 2001-336968P	P	20011107		
	US 2001-337017P	P	20011107		
	US 2002-363210P	P	20020307		
	US 2002-117937	A2	20020404		

AB Disclosed herein are methods for inducing an immunol. CTL response to an antigen by sustained, regular delivery of the antigen to a mammal so that the antigen reaches the lymphatic system. Antigen is delivered at a level sufficient to induce an immunol. CTL response in a mammal and the level of the antigen in the mammal's lymphatic system is maintained over time sufficient to maintain the immunol. CTL response. Also disclosed is an article of manufacture for delivering an antigen that induces a CTL response in an animal. The antigen can be used in vaccines for cancer or infection.

L4 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 1
AN 2002404319 MEDLINE
DN PubMed ID: 12153331
TI Potential new methods for antiepileptic drug delivery.
AU Fisher Robert S; Ho Jet
CS Stanford Comprehensive Epilepsy Center, Stanford University Medical Center, Stanford, California 94305-5235, USA.. rfisher@stanford.edu
SO CNS drugs, (2002) 16 (9) 579-93. Ref: 125
Journal code: 9431220. ISSN: 1172-7047.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020803
Last Updated on STN: 20021017
Entered Medline: 20021016
AB Use of novel drug delivery methods could enhance the efficacy and reduce the toxicity of antiepileptic drugs (AEDs). Slow-release oral forms of medication or depot drugs such as skin patches might improve compliance and therefore seizure control. In emergency situations, administration via rectal, nasal or buccal mucosa can deliver the drug more quickly than can oral administration. Slow-release oral forms and rectal forms of AEDs are already approved for use, nasal and buccal administration is currently off-label and skin patches for AEDs are an attractive but currently hypothetical option. Therapies under development may result in the delivery of AEDs directly to the regions of the brain involved in seizures. Experimental protocols are underway to allow continuous infusion of potent excitatory amino acid antagonists into the CSF. In experiments with animal models of epilepsy, AEDs have been delivered successfully to seizure foci in the brain by programmed **infusion pumps**, acting in response to computerised EEG seizure detection. Inactive prodrugs can be given systemically and activated at the site of the seizure focus by locally released compounds. One such drug under development is DP-VPA (or DP16), which is cleaved to valproic acid (sodium valproate) by phospholipases at the seizure focus. Liposomes and nanoparticles are engineered micro-reservoirs of a drug, with attached antibodies or receptor-specific binding agents designed to target the

particles to a specific region of the body. Liposomes in theory could deliver a high concentration of an AED to a seizure focus. Penetration of the blood-brain barrier can be accomplished by linking large particles to iron transferrin or biological toxins that can cross the barrier. In the near future, it is likely that cell transplants that generate neurotransmitters and neuromodulators will accomplish renewable endogenous drug delivery. However, the survival and viability of transplanted cells have yet to be demonstrated in the clinical setting. Gene therapy also may play a role in local drug delivery with the use of adenovirus, **adeno-associated virus**, herpesvirus or other delivery vectors to induce brain cells to produce local modulatory substances. New delivery systems should significantly improve the therapeutic/toxic ratio of AEDs.

L4 ANSWER 5 OF 11 MEDLINE on STN
AN 2002453940 MEDLINE
DN PubMed ID: 12208666
TI Peripheral but not central leptin prevents the immunosuppression associated with hypoleptinemia in rats.
AU Zhang Y; Wilsey J T; Frase C D; Matheny M M; Bender B S; Zolotukhin S; Scarpace P J
CS Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Gainesville, FL 32608-1197 USA.
NC AG 17047 (NIA)
SO Journal of endocrinology, (2002 Sep) 174 (3) 455-61.
Journal code: 0375363. ISSN: 0022-0795.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200211
ED Entered STN: 20020906
Last Updated on STN: 20021212
Entered Medline: 20021108
AB Leptin is a peripheral immunoenhancing reagent that directly activates splenic lymphocytes in mice. We found that a 48 h fast in rats resulted in a decrease in serum leptin that was accompanied by a lower delayed-type hypersensitivity (DTH) response. Peripheral leptin replacement completely restored this response in fasted animals. We employed a recombinant **adeno-associated virus** (rAAV) system to deliver leptin gene directly into rat brain to assess the effect of sustained long-term central expression of leptin on immune responses. The rAAV-leptin rats had elevated central leptin over the 60 day duration of the experiment, whereas body fat and circulating leptin fell to near zero levels. The DTH response was significantly reduced by 10-20% in rats receiving rAAV-leptin compared with the control rats, and the difference was maintained for over 50 h. When the rats undergoing rAAV-leptin gene therapy were given either murine recombinant leptin or PBS s.c., rats receiving leptin had a 17% higher DTH response than rats receiving PBS. The isolated splenocytes from the former group also proliferated 34% more in vitro in response to the mitogen concanavalin A as compared with the latter group. These results suggest that peripheral leptin has a dominant role in maintaining T-cell-mediated immune responses in rats, and central leptin is unable to compensate for the immunosuppression associated with peripheral hypoleptinemia. Furthermore, preservation of normal cell-mediated immune responses does not require fat tissue as along as serum leptin levels are maintained.

L4 ANSWER 6 OF 11 MEDLINE on STN
AN 2002631711 MEDLINE
DN PubMed ID: 12389290
TI Gene therapy for spinal applications.
AU Hidaka Chisa; Khan Safdar N; Farmer James C; Sandhu Harvinder S
CS Hospital for Special Surgery, Belfer Gene Therapy Core Facility, Weill

Medical College of Cornell University, New York, NY, USA.. hidakac@hss.edu
SO Orthopedic clinics of North America, (2002 Apr) 33 (2) 439-46. Ref: 76
Journal code: 0254463. ISSN: 0030-5898.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200211
ED Entered STN: 20021023
Last Updated on STN: 20021213
Entered Medline: 20021106
AB Gene therapy is a promising drug delivery mechanism for the treatment of spinal disorders. Currently, the technique has been most useful in enhancing growth factor therapy for spinal fusion, intervertebral disc regeneration, and spinal cord injury healing. Gene therapy allows for the high-level local production of growth factors, obviating the need for slow release carriers or continuous **infusion pumps** that are otherwise necessary because of the short half-lives of most peptide growth factors. Although continuous expression is desirable, growth factor therapy is usually intended to be transient. The typical expression profile of Ad vectors--at a high level over 2 weeks or so--has been ideal, leading to its widespread use in these applications. Despite the ability of Ad to deliver genes directly in vivo, however, the cell-based ex vivo approach has been used widely in spinal applications. In spinal cord injury, cells such as peripheral nerve or Schwann cells may provide a permissive substrate for axonal growth [51]. For spinal fusion and IVD regeneration, ex vivo manipulation of cells facilitates gene transfer, because bone and IVD tissue are too dense to be penetrated by injection of Ad or other vectors. The use of cells may be advantageous in these applications in which new tissue formation is the goal. Finally, the use of genetically modified cells may decrease the inflammatory reaction induced by Ad vectors. Although gene therapy for spinal disorders has been centered around Ad-mediated transfer of single growth factor genes, the options for candidate genes and vectors are growing rapidly. Ad vectors are being improved by decreasing their immunogenicity and altering their tropism [2]. Vectors based on other viruses (such as herpes, **adeno-associated virus**, and lentivirus) are being developed, also with lower immunogenicity and with longer durations of expression [26,67]. Regulated expression, such as with the tetracycline regulated promoter, is being developed so that genes can be turned on or off as needed. Such regulation may be sensitive even to physiologic cues in the future [68,69]. Finally, the high throughput technologies, such as the gene chip, are elucidating thousands of genes that may be good candidates for the enhancement of bone healing and IVD and spinal cord regeneration. Genes whose products not only support bone, fibrocartilage, or axon growth but also neutralize natural inhibitors or promote tissue remodeling and maturation may be good future candidates. In the future, a series of vectors with multiple genes that are regulated by physiologic cues might be used to enhance spinal fusion, restore IVD tissue, or support spinal cord healing.

L4 ANSWER 7 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AN 2002:520392 SCISEARCH
GA The Genuine Article (R) Number: 566BZ
TI Current issues in cochlear gene transfer
AU Lalwani A K (Reprint); Jero J; Mhatre A N
CS Univ Calif San Francisco, Dept Otolaryngol Head & Neck Surg, Epstein Labs, Lab Mol Otol, 533 Parnassus Ave, U490A, San Francisco, CA 94143 USA (Reprint); Univ Calif San Francisco, Dept Otolaryngol Head & Neck Surg, Epstein Labs, Lab Mol Otol, San Francisco, CA 94143 USA; Univ Calif San Francisco, Dept Otolaryngol Head & Neck Surg, Div Otol Neurotol & Skull Base Surg, San Francisco, CA 94143 USA; Univ Helsinki, Cent Hosp, Dept

Otolaryngol, FIN-00290 Helsinki, Finland
CYA USA; Finland
SO AUDIOLOGY AND NEURO-OTOLOGY, (MAY-JUN 2002) Vol. 7, No. 3, pp. 146-151.
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.
ISSN: 1420-3030.
DT Article; Journal
LA English
REC Reference Count: 20
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Cochlear gene therapy represents a potential experimental and therapeutic tool to understand and treat deafness. In designing cochlear gene transfer studies, the chosen route of delivery of vector and the choice of gene therapy vector have to be given careful consideration. Several different routes of delivery have been tested in our laboratory including **infusion** with **osmotic** mini-**pump**, direct microinjection into the cochlea and application of vector-transgene complex-soaked Gelfoam into the direct contact with the round window membrane. In our experience, the latter is an easy, safe and atraumatic technique to deliver gene into the cochlea. A number of different gene transfer vectors have been investigated in vivo for their efficacy, utility and safety in intracochlear gene transfer. Vectors successfully studied include cationic liposomes, **adeno-associated virus**, adenovirus, lentivirus, herpes simplex virus and vaccinia virus. While the viral vectors offer clear experimental advantages, human gene therapy in the future will likely utilize nonviral vectors to maximize safety. Finally, safety issues regarding dissemination of gene transfer vectors beyond the target cochlea will need to be adequately addressed. Copyright (C) 2002 S. KargerAG, Basel.

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:844926 CAPLUS
DN 135:366764
TI Method of controlling L-dopa production and of treating dopamine deficiency
IN Mandel, Ronald J.; Leff, Stuart E.
PA Cell Genesys, Inc., USA
SO U.S., 13 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6319905	B1	20011120	US 1999-314790	19990519
PRAI US 1998-114016P	P	19981229		

AB The present invention provides an effective approach to achieve the tightly modulated production of L-DOPA and/or dopamine at a preselected target location in the brain of a mammal by combining gene therapy approaches to supply a key enzyme in the synthesis of L-DOPA such as tyrosine hydroxylase, and novel drug delivery modalities to administer a uniform level of a modulator of the activity of such key enzyme. The fine-tuned administration of the modulator establishes continuously uniform levels of modulator which in turn allow the effective modulation of L-DOPA and/or dopamine levels at a preselected target location in the brain of the mammal.
RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:22879 BIOSIS
DN PREV200200022879
TI **Adeno-associated viral** delivery of GDNF protects striatal neurons in a rat model of Huntington's Disease.
AU McBride, J. L. [Reprint author]; Chen, E. Y. [Reprint author]; Leventhal,

L. [Reprint author]; During, M. J.; Kordower, J. H. [Reprint author]
CS Neurological Sciences, Rush-Presbyterian, St Luke's Med Ctr, Chicago, IL, USA
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2574. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Dec 2001
Last Updated on STN: 25 Feb 2002
AB Huntington's Disease is a genetic disorder leading to the degeneration of striatal-output neurons. Although no treatment is currently available for this disorder, many neurotrophic factors have been shown to increase the survival of striatal neurons. Intraventricular infusion of Glial cell line-Derived Neurotrophic Factor (GDNF) has been shown to be restorative for striatal neurons following Quinolinic Acid lesions in rodents. The present study investigated the neuroanatomical effects of **adeno-associated viral** delivery of the GDNF gene (AAV-GDNF) in a different rat model of Huntington's Disease. Two groups of Lewis rats received stereotaxic, bilateral injections of either AAV-GDNF (n=7) or AAV-Green Fluorescence Protein (AAV-GFP; n=7) into the striatum. One week later, rats were subcutaneously implanted with mini-**osmotic pumps** containing the mitochondrial toxin, 3-Nitroproprionic Acid (40 mg/kg). All rats were sacrificed one week post-**osmotic pump** surgery. Histological analysis revealed that NeuN-immunoreactive striatal neurons were protected in rats treated with AAV-GDNF. Rats in the AAV-GDNF group exhibited significant increases in neuronal number (45%) and density (38%) in the striatum ($p<.001$) compared to rats treated with AAV-GFP. These data indicate that the viral-mediated transfer of the GDNF gene prevents the structural consequences of 3-NP lesion and may be a viable treatment for Huntington's Disease.

L4 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 2
AN 2001176319 MEDLINE
DN PubMed ID: 11144956
TI Distribution of AAV-TK following intracranial convection-enhanced delivery into rats.
AU Cunningham J; Oiwa Y; Nagy D; Podsakoff G; Colosi P; Bankiewicz K S
CS Avigen, Inc., Alameda, CA, USA.
SO Cell transplantation, (2000 Sep-Oct) 9 (5) 585-94.
Journal code: 9208854. ISSN: 0963-6897.
CY United States
DT (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329
AB **Adeno-associated virus** (AAV)-based vectors are being tested in animal models as viable treatments for glioma and neurodegenerative disease and could potentially be employed to target a variety of central nervous system disorders. The relationship between dose of injected vector and its resulting distribution in brain tissue has not been previously reported nor has the most efficient method of delivery been determined. Here we report that convection-enhanced delivery (CED) of 2.5 x 10(8), 2.5 x 10(9), or 2.5 x 10(10) particles of AAV-thymidine kinase (AAV-TK) into rat brain revealed a clear dose response. In the high-dose group, a volume of 300 mm3 of brain tissue was partially transduced. Results showed that **infusion pump** and

subcutaneous **osmotic pumps** were both capable of delivering vector via CED and that total particle number was the most important determining factor in obtaining efficient expression. Results further showed differences in histopathology between the delivery groups. While administration of vector using **infusion pump** had relatively benign effects, the use of **osmotic pumps** resulted in notable toxicity to the surrounding brain tissue. To determine tissue distribution of vector following intracranial delivery, PCR analysis was performed on tissues from rats that received high doses of AAV-TK. Three weeks following CED, vector could be detected in both hemispheres of the brain, spinal cord, spleen, and kidney.

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:55483 CAPLUS
DN 128:97727
TI Transformation and gene therapy of cells of the inner ear
IN Lalwani, Anil; Schindler, Robert A.
PA Regents of the University of California, USA; Lalwani, Anil; Schindler, Robert A.
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9800014	A1	19980108	WO 1997-US11602	19970627
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9735915	A1	19980121	AU 1997-35915	19970627
PRAI US 1996-674231		19960628		
WO 1997-US11602		19970627		

AB Compns. and methods are disclosed for transformation of cells of the inner ear and treatment of conditions of the inner ear using such methods. More specifically, cells of an inner ear of a subject are genetically altered to operatively incorporate a nucleotide sequence which expresses a gene product of interest (e.g., a therapeutic gene product). Preferably, the inner ear cell into which the DNA of interest is introduced and expressed is a cell of the cochlea, more preferably a cell of the spiral ligament, spiral limbus, stria vascularis, organ of Corti, spiral ganglion, and/or Reissner's membrane, and/or an auditory hair cell. The DNA of interest, preferably present within an **adeno-assocd.** **viral** vector, is introduced through a cannula inserted in the round or oval window and in communication with the perilymph or endolymph. Preferably, introduction of the DNA of interest is accomplished using an osmotic minipump.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>